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TITLE:
Developing Treatment, Treatment Validation, and Treatment Scope in the Setting of an Autism Clinical Trial

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14. ABSTRACT

The first year of the project has been used to obtain IRB approval from the UMDNJ-RWJMS IRB office. We obtained IRB approval on December 7th, 2009. Our approved protocol and supporting documents have been submitted to the Human Research Protection Office (HRPO) Office of Research Protections (ORP) of the DOD for review. We are also in the process of applying for a Certificate of Confidentiality from the NIH as per our IRB requirements. No Human Subjects Work will be done until we receive either a COC or a letter indicating we do not need one. Once we have approval from the Human Research Protection Office (HRPO) Office of Research Protections (ORP) of the DOD we will begin work on tasks 2 through 7. Please see initiating project W81XWH-081-0728 and partnering project W81XWH-08-1-0729.

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Introduction:

This project is to test to see if DHA treatment can beneficially affect excretion of urinary biomarkers of oxidative stress and the autism clinical phenotype. In addition polymorphic variants of genes of certain enzymes that synthesize and metabolize docosahexaenoic acid (DHA) may contribute to the phenotype of some autism cases. We will test to see if any of these genes are risk factors for autism. We will also measure changes in excretion of the polyunsaturated fatty acid (PUFA) derived biomarkers of oxidative stress (isoprostanes and neuroprostanes) together with the changes in production of anti-inflammatory lipid mediators. We will test these biomarkers to see if we can monitor and validate effectiveness of DHA therapy. We will also test the genotypes of key DHA-metabolizing enzymes can predict which patients will respond to therapy.
Please see initiating project W81XWH-08-1-0728 and partnering project W81XWH-08-1-0729.

Body:

Project 1: PI Sherie Novotny, MD, Partnering PI, W81XWH-08-1-0730

Please see initiating project W81XWH-08-1-0728 and partnering project W81XWH-08-1-0729.

Task 1 Full board review with pending IRB approval prior to beginning (4-6 months, S. Novotny).

The first year of the project has been used to obtain IRB approval from the UMDNJ-RWJMS IRB office. The major points in the timeline follow. In the course of this timeline numerous meetings took place with the IRB office, the Chairpersons of the three PI's of this project, and the Research Dean in order to facilitate the process. In addition we consulted with a number of persons with expertise in the field.

Our initial submission to our IRB office was submitted on July 18th 2008. We received a de-briefing memo from our IRB on August 4th 2008 with twenty one suggestions and recommendations.

We responded to this memo on September 15th 2008. The IRB requested clarification to one of our responses. This clarification was sent in on November 5th, 2008. Our IRB offices were moved in the month of October 2008 and their review was not completed until November.

We received a "Notice of Approval with Stipulations" from the IRB on November 26th, 2008 and we received the stipulations themselves on December 5th, 2008. We responded to all four stipulations and sent the responses to the IRB on December 22nd, 2008. An expedited review was scheduled for January 9th, 2009. The reviewer decided that our response to the first stipulation (related to simplification of the language in the consent form) should be reviewed by a full committee. The committee met on January 30th, 2009 and we received the memo on February 6th, 2009. At this meeting our four responses were tabled, and 24 suggestions / recommended changes were sent to us, most of them completely new. One of these changes requested was that we obtain an IND for the use of DHA.

We responded to this by sending our IRB copies of documentation to support that an IND was not needed because 1.) an FDA letter dated May 17, 2001 to Martek (manufacturers of the DHA to be used) designated their DHA as "Generally Regarded as Safe" (GRAS) (please see http://www.cfsan.fda.gov/~rdb/opa-g041.html) and 2.) documentation from the FDA on their

website www.clinicaltrials.gov (search for MARTEK and DHA) shows that none of the 10 current or completed studies that used Martek's DHA had had an IND including one with subjects with autism (showing that our use was not a new indication). We responded to the other 23 new questions and submitted all this for review on February 27th, 2009.

We received the de-briefing memo on March 6th, 2009. The memo requested that we needed to get an IND from the FDA for the project and it contained 2 new additional requirements. First, our IRB wanted us to create a tissue bank for the storage of the samples. Second our IRB wanted us to apply for a Certificate of Confidentiality for this project before they would give full approval.

We convened a meeting with the Chair of the IRB, the IRB director and the PI's on May 8th, 2009 to discuss each of their requirements.

The key outcomes of the meeting and our responses were as follows;
First, even though it is already considered General Regarded as Safe (GRAS) in children, we would nonetheless need either an IND for the use of Martek's DHA or a letter from the FDA saying that one was not needed. We completed the application for the IND and we submitted it on July 16th, 2009 (available upon request, 298 pages). We received a letter from the FDA August 4th, 2009 exempting us from needing an IND.
Second, even though to our knowledge there is no federal or state rule or regulation requiring us to create a tissue bank and there was no university policy in place, a Tissue Bank Application, Protocol and Manual along with supporting documents would have to be submitted for this project. Upon receipt of the March 6th memo asking us to set up a tissue bank we decided to take two parallel tracks. The first was to write a Tissue Bank Application. The second was to present to the IRB that we would destroy the samples after the termination of the project, and if at that time there was future scientific use for the samples and a tissue bank was available we would amend the protocol and place the samples in a bank. We submitted a Tissue Bank application on May 24th 2009. We have since completely re-written the Tissue Bank Application, Protocol, Manual and supporting documents and are preparing to re-submit.

Third, our IRB told us that we must apply for a Certificate of Confidentiality (COC) before they would give us full approval. Prior IRB approval is a NIH requirement for submitting a COC application.

Additional submissions, responses and amendments.
The following dates represent requests for changes or requests for clarifications (to either the consent form, assent form, protocol, application or other supporting documentation) and subsequent replies by us;

Memo from the IRB	May 29, 2009	Replied to on July 10th, 2009
Memo from the IRB	September 1, 2009	Replied to on September 9th, 2009
Memo from the IRB	September 30th, 2009	Replied to on October 19, 2009
Memo from the IRB	November 20th, 2009	Replied to on December 5th, 2009

In addition there were 3 modifications to the protocol, all related to changes in study personnel between the time the grant was submitted and the time the study was approved.

We obtained IRB approval on December 7th 2009. Two important points. First our IRB office accepted the FDA's letter stating that we do not need an IND. Second, our IRB office also accepted our proposal to destroy the samples at the end of the project. We are continuing with

the Tissue Bank application and once approved we will amend the protocol for this project to allow us to keep the samples by placing them into the Tissue Bank.

Our approved protocol and supporting documents have been submitted to the Human Research Protection Office (HRPO), Office of Research Protections (ORP) of the DOD for review. We are also in the process of applying for a Certificate of Confidentiality from the NIH as per our IRB requirements. No work will be done on the recruited subjects until we receive either a COC or a letter indicating we do not need one and we have approval from the Human Research Protection Office (HRPO), Office of Research Protections (ORP) of the DOD.

Task 2 Volunteers recruited from local clinics, support groups and advocacy groups (6-30 months).Forty four child or adolescent outpatients per year with age ranges from 5-17, for three years totaling 132 patients, will be randomized into the 12-week double-blind, placebo-controlled parallel treatment study.

This task has not begun yet. This will start once the NIH has awarded the project a COC or sent us a letter telling us we do not need one.

Task 3 Informed consent/assent obtained (6-30 months).

This task has not begun yet. This will start once recruitment starts.

Task 4 Full diagnostic assessment with Autism Diagnostic Interview-revised (ADI-R), Autism Diagnostic Observation Scale (ADOS), Vineland Adaptive behavior scale and Leiter Intelligence Scale (E Roberts); DSM IV criteria (S. Novotny) for eligibility & diagnosis. Parents will complete baseline Aberrant Behavior Checklist; study psychiatrist will complete Clinical Global Improvement, baseline Severity Scale (6-30 months).

This task has not begun yet. This will start once recruitment starts.

Task 5 Cases undergo full medical evaluation to determine health; at this visit will have phlebotomy including 10 mls for blood chemistry, PT/PTT, hematology, 10 ml for genotyping (Project III), urine for pregnancy test, drug screen as indicated, routine urinalysis; urine collected for Project II.

This task has not begun yet. This will start once recruitment starts.

Task 6 Cases randomized to receive either DHA, 200mg daily, or placebo. Cases given DHA after physical exam and routine lab-work completed.

This task has not begun yet. This will start once recruitment starts.

Task 7 Cases seen weekly for four weeks and biweekly for the remaining 8 weeks. Aberrant Behavior Checklist done every 4 weeks and at termination and Clinical Global Improvement Scale done every 2 weeks and at termination.

This task has not begun yet. This will start once recruitment starts.

Task 8 Cases complete the study with repeat ADOS, Vineland Adaptive Behavior Scale (E Roberts) and Aberrant Behavior checklist (parent) and Clinical Global Improvement Scale (S

Novotny). Blood work for safety measures; urine will be collected for Project II during last week of DHA or placebo.

This task has not begun yet. This will start when treatment starts..

Task 9 Data will be collected and analyzed (6-36 months, S Buyske).

This task has not begun yet. This will start once when analysis of samples is completed.

Task 10 Manuscripts prepared and submitted for publication (03 year, all investigators)

This task is to be done when the analysis of the data is completed.

Key Research Accomplishments

There are no Key Research Accomplishments yet.

Reportable Outcomes:

There are no reportable outcomes for any of the three projects as of yet.

Conclusion:

A large amount of time was spent on getting IRB approval for this project. We received a conditional IRB approval on December 7th 2009. The condition is to apply to NIH for a Certificate Of Confidentiality (COC). We have written a COC and plan on submitting by the end of the week. We have also, submitted the approved protocol and supporting documents to the Human Research Protection Office (HRPO) Office of Research Protections (ORP)of the DOD for review. If the Human Research Protection Office (HRPO) Office of Research Protections (ORP) of the DOD requires no changes we will start recruiting subjects as soon as we have a COC. If changes must be made to the Protocol or supporting documents we will amend our protocol with our IRB and upon acceptance of the amendment by our IRB and receipt of the COC we will begin recruiting subjects, Task 2. Once recruitment has started we will begin tasks 3 – 7. We anticipate no potential problems that would impede progress in recruiting the subjects. In fact we expect that we can move forward rather quickly. We constantly receive phone calls from parents that would like to enroll their child in this study. In addition our past experience suggests that the parents of the individuals with autism will be eager to have their children participate in this project.

References:

There are no references.

Appendices:

There are no appendices.